Adrenal Glands: medulla

- Contains Chromaffin cells which are modified postganglionic sympathetic neurons
- They are activated by sympathetic nerve fibers
- The cells secrete the catecholamines epinephrine and norepinephrine:
  - 75-85% of what is secreted in epinephrine
  - 15-25% is norepinephrine

- Epinephrine works on heart and metabolic activities while norepinephrine is more of a peripheral vasoconstrictor

- Stress activates the sympathetic nervous system which thus induces the medulla to release the catecholamines.
The Stress Response

- Stress = any condition that threatens homeostasis
- GAS (General Adaptation Syndrome) is our bodies response to stress-causing factors
- Three phases to GAS
  - Alarm phase (immediate, fight or flight, directed by the sympathetic nervous system)
  - Resistance phase (dominated by glucocorticoids)
  - Exhaustion phase (breakdown of homeostatic regulation and failure of one or more organ systems)
The Stress Response

Resistance Phase
Long-term metabolic adjustments

1. Mobilization of remaining energy reserves: Lipids are released by adipose tissue; amino acids are released by skeletal muscle.
2. Conservation of glucose: Peripheral tissue (except neural) breaks down lipids to obtain energy.
3. Elevation of blood glucose concentrations: Liver synthesizes glucose from other carbohydrates, amino acids, and lipids.

Adrenal cortex
Renin
Angiotensin

KEY
GH = Growth hormone
GC = Glucocorticoids
ACTH = Adrenocorticotropic hormone
MC = Mineralocorticoids (aldosterone)
ADH = Antidiuretic hormone

The Stress Response

Two-System View of Stress Response
The Stress Response

Growth Hormone (GH)

- Is a protein of ~ 191 AA long
- Structure related to Prolactin as it originates from similar ancestral gene
- Secreted by somatotropes which constitute the majority of the cells in the APG
Growth Hormone (GH)

Growth Hormone has a dual action

- promotes growth of hard (bone) & soft tissue (cell division and increase in size)
- influences metabolism

Although GH can affect all cells, the major target cells are

- Skeletal Bones
  - It stimulates the epiphyseal plates of bones
  - Long term effect is that it prolongs the growth of bones.

- Skeletal muscle.
  - Its effect on skeletal tissue result in increased muscle mass.

Growth Hormone (GH)

GH works via a direct and indirect effect.

- The direct action is “anti-insulin” like effect
- The indirect effect is an “insulin-like” effect
Direct Effect of GH

Muscle

Liver

Adipose Tissue

Glucose Uptake

Gluconeogenesis

Protein Synthesis

Blood plasma levels

Glucose

A.A.

F.F.A

Indirect Effects of Growth Hormone (GH)

GH stimulates the release of small proteins from the liver and other tissues

These proteins are growth promoting proteins and are called Somatomedins or Insulin-like growth factors (IGF's).

Actions of the IGF's

• Promote protein synthesis/cell proliferation in most tissues

• Maintains thickness of epiphyseal plates at the end of long bones, thus maintains bone growth
The immediate metabolic effect is thus that blood glucose and fatty acid levels increase.

The targeted tissues will use the fatty acids as fuel while the glucose is spared for use by the non-affected tissues e.g. the brain which only uses glucose.

The overall effect is to promote accumulation of lean body mass.
Control of GH secretion

Two hypothalamic Hormones are involved in the control of GH secretion:

**GH releasing hormone (GHRH) or Somatocrinin.**
- Low plasma glucose
- Low plasma FFA
- High plasma AA’s
  
  Induce release of GHRH

**GH inhibiting hormone (GHIH) or Somatostatin**
- High plasma glucose
- High plasma FFA’s
- Low plasma AA’s
- Obesity
  
  Induce release of GHIH

Besides the two hypothalamic hormones, regular negative feedback mechanisms are at play:

- Too much GH itself will ‘shut’ down the release of GHRH from the HT.
- Too much GH will result in a high level of IGF’s, they will shut down both the release of GHRH from H.T. and GH from APG.
**Control of GH secretion**

- There is a pattern of release of GH during our life, with a peak occurring during puberty. After that it slowly decreases with age.

- GH release is also influenced by stress, exercise, sleep, fasting

**Hormones and growth**

- Normal growth requires the interaction of several endocrine organs
- Six hormones are important
  - GH
  - Thyroid hormones
  - Insulin
  - PTH
  - Calcitriol
  - Reproductive hormones
### Abnormalities in GH Output

#### Hypo-secretion of GH

During childhood
- slow bone growth, premature closure of the epiphyseal plate
- **pituitary dwarfism**
- can be corrected with administration of GH early on

#### Hyper-secretion of GH

During childhood
- results in gigantism or gigantism

During adulthood
- results in **acromegaly**
  - bones in fingers, hand feet face grow (deformation of facial looks)
  - soft tissues thicken
  - usually results from a tumor in pituitary gland

Cure?
- hypophysectomy
- administration of synthetic analogues of somatostatin
Abnormalities in GH Output

Acromegaly of hands
(right hand is normal hand)

At 8 feet 8 inches he weighed 480 pounds and wore a size 36 shoe. He had the appropriate job of advertising for a shoe company.

In kindergarten he was already 5'6" tall
He died at the age of 32 (1940)

Robert Wadlow

Pakistani “tall man”
NEW Extra Strength HGH liquid helps restore somatotropin levels and wash away the effects of age!

Human Growth Hormone (somatropin), supplementation may enhance the growth of cells, bones, muscles and organs throughout the body.

Moderate Weight Loss, Increased Strength, More Energy, Better Sleep, and Enhanced Sexual Function are often–seen homeopathic HGH results during the first two months.

The Pancreas

Pancreas is a mixed gland containing endocrine as well as exocrine cells

• Acinar cells are the exocrine cells which produce digestive enzymes

• Other cells are organized in Islets of Langerhans: they contain 4 types of cells
  • alpha cells: produce/secrete the hormone glucagon
  • beta cells: produce/secrete the hormone insulin
  • delta cells: produce and secrete GH-IH
  • F cells: produce and secrete pancreatic polypeptide
The Pancreas

Both Insulin and Glucagon are important in the overall blood glucose balance during meals and in-between meals or fasting.

GLUCAGON

- 29 Amino Acid long peptide and a hyperglycemic hormone
- Promotes breakdown of liver glucogen into glucose units (= glycogenolysis)
- Promotes the release of glucose into the blood stream from the liver
- Promotes synthesis of glucose from lactic acid, proteins and fatty acids (gluconeogenesis)
- Secretion is prompted by low blood sugar levels and inhibited by high sugar levels.
The Pancreas

**INSULIN**

Insulin is a 51 Amino Acid peptide, synthesized from a proinsulin polypeptide chain. The final insulin consists out of two chains linked together by disulfide (S-S) bonds.

Insulin production involved intermediate steps. Initially, it is formed as pre-proinsulin, an inactive form that is secreted into the endoplasmic reticulum.

Post-translational processing clips the N-terminal signal sequence and forms the disulfide bridges, creating pro-insulin.

Pro-insulin is finally clipped at two positions to release the intervening C chain. This and active insulin are finally packaged into secretory granules for storage.
Insulin release is promoted by rising blood glucose levels.
- Glucose is taken up into beta cells by a GLUT2 transporter.
- This increases mitochondrial action and ATP/ADP ratios increase.
- Increased levels of ATP inactivate a K⁺ channel, resulting in depolarization of the cell membrane.
- This in turn opens Ca²⁺ channels and the influx of Ca²⁺ results in exocytosis of the insulin vesicles.

Main effect is to lower blood glucose levels
- Does so by enhancing membrane transport of glucose into the muscle cells, adipocytes and liver by increasing GLUT4 transporters in their cell membranes

- Insulin also triggers
  - Net glycogen synthesis
  - Amino acid uptake and protein in muscle
  - Converts glucose into fats in adipose tissues and liver
INSULIN

Secretion of insulin is thus triggered by high blood glucose, but high A. A. levels, high fatty acid levels also induce insulin secretion.

In addition, the action of hormone that increase blood glucose, will trigger insulin release; examples are Glucagon - Thyroxine - Growth Hormone - Cortisol - Epinephrine.

• Too much insulin would result in hypoglycemia.

• As one step in monitoring insulin levels, the enzyme insulinase (found in the liver and kidneys) breaks down blood-circulating insulin resulting in a half-life of about six minutes for the hormone.

• This degradative process ensures that levels of circulating insulin are modulated and that blood glucose levels do not get dangerously low.
### Clinical Aspect: Diabetes mellitus

Results from hyposecretion or hypoactivity of insulin

Overall result is that:

- **blood glucose is not** absorbed into the cells and blood glucose levels rise
- **Fats are used** for energy source but breakdown results in excess Acetyl CoA which is converted into **ketone bodies**
- Ketone bodies are acidic and results in **ketoacidosis**; blood pH drops
- Results in increase in breathing to blow off CO₂ but if persists, acidosis may inhibit many physiological processes

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### Clinical Aspect: Diabetes mellitus

When fat and carbohydrate oxidation (use) are balanced, acetyl-CoA from fat breakdown enters TCA cycle.

When fat breakdown dominates (in fasting or diabetes), OxaloAcetate (OAA) is shunted away by gluconeogenesis to make glucose

- Not enough [OAA] present to combine with all low acetyl-CoA to form citrate and enter TCA
- Instead, acetyl-CoA forms “ketone bodies” via ketogenesis
Clinical Aspect: Diabetes mellitus

Table 17-2: Ketone Body Accumulation in Diabetic Ketosis

<table>
<thead>
<tr>
<th></th>
<th>Urinary excretion (mg/24 h)</th>
<th>Blood concentration (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤125</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Extreme ketosis</td>
<td>5,000</td>
<td>90</td>
</tr>
<tr>
<td>(untreated diabetes)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Aspect: Diabetes mellitus

Three cardinal signs of diabetes mellitus:

- Polyuria:
  - Excess urine formation due to excess glucose which spills over in urine and drags water with it.
  - Ketones spill over as well and since they are negatively charged, they drag electrolytes with them.
- Polydipsia: person feels extremely thirsty and drinks a lot because of the dehydration.
- Polyphagia: person tends to eat a lot.

Clinical Aspect: Diabetes mellitus

There are Two types of Diabetes:

A. Type I or Insulin-dependent diabetes mellitus (IDDM or T1DM)

- Due to an autoimmune disease that destroys the beta cells.
- Occurs usually before age 15 (juvenile onset diabetes).
- At early age person makes no insulin anymore and cells thus start using fats from fat breakdown.
- Results in high blood cholesterol and causes problems within vascular system.
- Symptoms in long run are arteriosclerosis, strokes, heart attacks, renal shut down, gangrene, blindness.
- Also effects nervous system and can result in loss of sensation, impotence, bladder problems.
- Although insulin injections overcome the immediate metabolic problems like acidosis, the long term problems are only delayed.
Clinical Aspect: Diabetes mellitus

B. Type II or NON-insulin dependent diabetes mellitus (NIDDM or T2DM)

- occurs usually after age 40 (mature onset diabetes)
- hereditary predisposition is striking, indicating a genetic link
- Type II patients produce insulin but don't have enough insulin receptors
- 90% of cases are overweight patients indicating a link between obesity and NIDDM as well
- Ketosis is not a major problem in this group and symptoms can be managed by weight loss and diet
- Due to unhealthy diet of the US population, it is now a major clinical health problem.
Other Hormone Systems

**HEART**
- Specialized muscle cells in the atria produce natriuretic peptides when blood pressure becomes excessive
- Generally oppose actions of angiotensin II (thus inhibit aldosterone release and cause diuresis)

**THYMUS**
- Produces thymosins
- Help develop and maintain normal immune defenses

**KIDNEYS - LUNGS**
- Produces RENIN and EPO
- Renin produces ANG I, which via ACE becomes ANG II

**ADIPOSE TISSUE**
- Produces LEPTIN and RESISTIN
- LEPTIN is important for appetite feedback control
- RESISTIN
  - Resistin inhibits adipocyte differentiation and may function as a feedback regulator of adipogenesis.
  - Administration of resistin to mice resulted in increased glucose production and blood glucose levels.
  - Therefore, resistin also functions as a regulator of glucose homeostasis and a physiologic antagonist to hepatic insulin action.
Hormones often interact, producing:

- Antagonistic (opposing) effects
- Synergistic (additive) effects
- Permissive effects (one hormone is required for the other to produce its effect)
- Integrative effects (hormones produce different but complimentary results)